



Case Series

Clinical Outcomes of Orchiopexy for Undescended Testes in Syndromic Patients with Developmental Delay, Genetic Syndromes, and Congenital Anomalies

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Abstract

Objectives: To determine patient characteristics and clinical outcomes during and after orchiopexy in syndromic children with either developmental delay, genetic syndromes, or congenital anomalies compared to age matched controls. **Study Design:** This is a retrospective cohort study of patients ≤ 18 years old who underwent orchiopexy at UCSF Benioff Children's Hospitals between 2012-2020 and were identified as syndromic patients with either developmental delay, molecular testing-confirmed genetic syndromes or known congenital anomalies, compared to an age-matched non syndromic control group. Intra-operative covariates including procedure staging, surgical approach, undescended testes location, estimated blood loss, intra-operative complication occurrence, orchiopexy laterality and post-operative covariates including complication occurrence were gathered through electronic chart review. Differences in continuous and categorical variables were assessed using Mann-Whitney and Chi-squared tests, respectively. **Results:** Our study yielded 825 total patients undergoing orchiopexy, of which 16% were defined as syndromic. 67 patients had developmental delay, 38 patients had a defined genetic syndrome, and 25 patients had an associated congenital anomaly. These patients were compared to 60 age matched non-syndromic control patients undergoing orchiopexy. Patients with unspecified developmental delay more often underwent bilateral orchiopexy compared to the control group (43% v. 23%, $p=0.02$). Patients with a genetic syndrome were less likely to have a single stage procedure (92% v. 100%, $p=0.03$) and more likely to undergo bilateral orchiopexy (45% v. 23%, $p=0.03$) compared to the control group. There were no differences in rate of bilateral orchiopexy and single stage procedures between patients with a congenital anomaly and the control group. There was no difference in intraoperative or post-operative complications or clinical outcomes between the three syndromic groups and control group. **Conclusions:** Clinical outcomes were no different between patients with syndromes undergoing orchiopexy compared to non-syndromic children. Patients with non-specific developmental delay or a genetic syndrome more often had bilateral orchiopexies. Patients with a genetic syndrome were also less likely to have a single stage procedure. Orchiopexy in syndromic patients undergoing orchiopexy is safe with comparable outcomes to non-syndromic patients.

Keywords: Orchiopexy; Testis; Syndromic; Outcomes; Pediatrics

Introduction

Cryptorchidism is one of the most common congenital anomalies occurring in 2-4% of full term males [1]. The prevalence drops to approximately 1% at 3 months of age consistent with approximately 2/3 of undescended testes undergoing spontaneous descent in the first three months of life [2]. Approximately 85% of patients with undescended testis are isolated defects without any known associated syndromes [3]. This leaves approximately 15% of patients where the undescended testis is associated with a specific syndrome. Close to 500 different syndromes linked to over 400 genes have been described in patients with cryptorchidism based on data available in the Online Mendelian Inheritance in Man website (OMIM: <https://www.ncbi.nlm.nih.gov/omim>). Many of these syndromes are associated with defects of the hypothalamic-pituitary-gonadal axis, characterized by reduced androgen production or androgen action [4-6]. Syndromic cryptorchidism is also associated with defects in the central nervous system (cerebral palsy), spinal canal (myelomeningocele), abdominal wall (Prune Belly syndrome) or musculoskeletal (omphalocele) system. [7, 8]. (reference Baker)

Treatment of cryptorchidism is focused on preserving testicular function, specifically fertility in patients with bilateral disease. [9-11]. Additional indications for orchiopexy include reducing cancer risk and facilitating cancer diagnosis by repositioning the undescended testis into the scrotum (reference). Orchiopexy can also prevent hernia, testicular torsion and reduce the risk of trauma in an undescended testis. Finally, repositioning an ectopic testis into the normal position in the scrotum allows a sense of patient (and family) wholeness and well-being, potentially avoiding future developmental issues.

The clinical characteristics and outcomes of patients with non-syndromic cryptorchidism is well described in the literature [10-12]. The clinical outcomes for syndromic patients undergoing orchiopexy with developmental delay, genetic syndromes, and congenital anomalies is not well characterized. Parents of such children often pursue orchiopexy as it may confer a sense of positive impact over the patient's complex medical circumstance. Despite this rationale coupled with other medical desires for preserved fertility and cancer surveillance, little is understood about the potential risks associated with orchiopexy in this syndromic cohort. This leads to a knowledge gap where appropriate risk-benefit assessments cannot be made for each child. Therefore, the goal of our study is to report on the outcomes of syndromic patients undergoing orchiopexy compared to non-syndromic patients. We hypothesize that syndromic patients with cryptorchidism would have similar outcomes to non-syndromic patients, and that

orchiopexy is safe in this unique group of patients.

Methods

Study Populations

The study was approved by the committee on human research at UCSF (IRB#: 20-31745). All patients \leq 18 years old who underwent orchiopexy at UCSF Benioff Children's Hospitals at Mission Bay and Oakland between 2012-2020 were identified by searching the patient care EPIC database. Patients were then divided into four groups based on evaluation of the electronic medical history: 1) those with developmental delay, 2) those with molecular testing-confirmed genetic syndromes, 3) those with known congenital anomalies, and 4) an age-matched control group that did not meet criteria for groups 1-3.

Covariates

Intra-operative covariates assessed included procedure staging, surgical approach, undescended testes location, estimated blood loss, intraoperative complications occurrence, and orchiopexy laterality. Post-operative covariates including complication occurrence were gathered through retrospective chart review. Statistical analysis to determine differences in continuous and categorical variables were assessed using Mann-Whitney and Chi-squared tests, respectively.

Results

Between 2012 and 2020, 825 patient underwent orchiopexy at UCSF Benioff Children's hospitals Mission Bay and Oakland. Of this initial cohort, 130 (16%) patients were found to meet criteria for one of the three syndromic groups (developmental delay, genetic syndrome, congenital anomalies). 67 patients were identified with unspecified developmental delay, Developmental delay included unspecified in 19, speech/language delay in 11, global developmental delay in 11, cerebral palsy in 10, neurologic lesions on 8, autism in 7, and motor delay in 1. 38 patients were identified with a defined molecular genetic syndrome. Trisomy 21/Down's in 9, Prader-Willi in 9, Diamond-Blackfan in 2, Noonan in 2, Phelan-McDermid in 2, Arginosuccinate Lyase Deficiency in 1, CLOVES in 1, Cornelia de Lange in 1, Gabrielle de-Vries in 1, IPEX in 1, Kabuki in 1, NF1 in 1, Russell Silver in 1, SPATA-5 in 1, Trisomy 2 in 1, Trisomy 8 in 1, Tuberous Sclerosis in 1, Williams-Beuren in 1, and Wolff-Hirschhorn in 1. 25 patients were identified with a known congenital anomaly. Disorders of sex development in 8, rare cancers in 3, VACTERL syndrome in 4, prune belly syndrome in 3, posterior urethral valves in 3, gastroschisis in 3 and multicystic dysplastic kidney in 1. 60 randomized, age-matched non-syndromic patients who underwent orchiopexy were included as a control group.

Patients with unspecified developmental delay more often

underwent bilateral orchiopexy compared to the control group (43% v. 23%, p=0.02) (Table 1). There were no other significant differences in intra-operative and post-operative covariates between developmentally delayed patients and the age-matched control cohort. Patients with a genetic syndrome were less likely to have a single stage procedure (92% v. 100%, p=0.03) and more likely to undergo bilateral orchiopexy (45% v. 23%, p=0.03) compared to the control group (Table 2). There were no other significant differences in intra-operative and post-operative covariates between patients with genetic syndromes and the age-matched control cohort. There were no differences in outcomes between patients with a congenital anomaly and the control group (Table 3). There was no difference in intra-operative complications or early post-operative complications between the three syndromic groups undergoing orchiopexy versus the control group (Tables 1-3).

	Developmental delay¹ (n=67)	Control (n=60)	p-value²
Age (mean (SD))	4.6 (4.3)	4.8 (5.3)	0.51
Intra-Operative			
1 Staged Procedure (n, %)	65 (97.0)	60 (100.0)	0.18
Open Surgical Approach (n, %)	57 (85.1)	50 (83.3)	0.87
Testes Located in Inguinal Canal (n,%)	61 (89.7)	53 (88.3)	0.49
Estimated Blood Loss (mean (SD))	2.3 (2.5)	2.5 (2.3)	0.48
Had complication (n, %)	0 (0)	0 (0)	N/A
Underwent bilateral orchiopexy (n, %)	29 (43.3)	14 (23.3)	0.02
Post-Operative			
Had complication (n, %) ³	3 (5.7)	4 (7.3)	0.73

Table 1: Intra-operative and post-operative course during orchiopexy in patients with developmental delay; Developmental delay includes unspecified, speech/language delay, global developmental delay, cerebral palsy, neurologic lesions, autism, motor delay, and congenital CMV infection sequelae; p-value indicates level of significance resulting from Mann-Whitney test for continuous variables and Chi-squared test for categorical variables; Complications included bleeding, pain, and/or infection beyond expected from normal clinical course.

	Genetic Syndrome¹ (n=38)	Control (n=60)	p-value²
Age (mean (SD))	3.9 (4.5)	4.8 (5.3)	0.58
Intra-Operative			
1 Staged Procedure (n, %)	35 (92.1)	60 (100.0)	0.03
Open Surgical Approach (n, %)	30 (78.9)	50 (83.3)	0.78
Testes Located in Inguinal Canal (n, %)	33 (89.2)	53 (88.3)	0.73
Estimated Blood Loss (mean (SD))	2.2 (2.0)	2.5 (2.3)	0.52
Had complication (n, %)	0 (0)	0 (0)	N/A
Underwent bilateral orchiopexy (n, %)	17 (44.7)	14 (23.3)	0.03
Post-Operative			
Had complication (n, %) ³	2 (5.7)	4 (7.3)	0.77

Table 2: Intra-operative and post-operative course during orchiopexy in patients with genetic syndromes; Genetic syndromes included Down, Prader-Willi, Diamond-Blackfan, Noonan, Phelan-McDermid, Arginosuccinate Lyase Deficiency, CLOVES, Cornelia de Lange, Gabrielle de-Vries, IPEX, Kabuki, NF1, Russell Silver, SPATA-5, Trisomy 2, Trisomy 8, Tuberous Sclerosis, Williams-Beuren, Wolff-

Hirschorn;p-value indicates level of significance resulting from Mann-Whitney test for continuous variables and Chi-squared test for categorical variables; Complications included bleeding, pain, and/or infection beyond expected from normal clinical course.

	Congenital anomalies¹ (n=25)	Control (n=60)	p-value²
Age (mean (SD))	5.0 (3.9)	4.8 (5.3)	0.45
Intra-Operative			
1 Staged Procedure (n, %)	24 (96.0)	60 (100.0)	0.12
Open Surgical Approach (n, %)	19 (76.0)	50 (83.3)	0.12
Testes Located in Inguinal Canal (n, %)	21 (84.0)	53 (88.3)	0.78
Estimated Blood Loss (mean (SD))	3.8 (4.3)	2.5 (2.3)	0.39
Had complication (n, %)	0 (0)	0 (0)	N/A
Underwent bilateral orchiopexy (n, %)	6 (24.0)	14 (23.3)	0.95
Post-Operative			
Had complication (n, %) ³	2 (8.7)	4 (7.3)	0.83

Table 3: Intra-operative and post-operative course during orchiopexy in patients with congenital anomalies; Congenital anomalies include hearing loss, multi-cystic dysplastic kidney, disorders of sexual development, XXYY syndrome, prune belly syndrome, posterior urethral valves, gastroschisis, rare cancers, acute lymphocytic leukemia, VACTERL syndrome; p-value indicates level of significance resulting from Mann-Whitney test for continuous variables and Chi-squared test for categorical variables; Complications included bleeding, pain, and/or infection beyond expected from normal clinical course.

Discussion

Approximately 16% of our cohort of patients undergoing orchiopexy had either developmental delay, a defined genetic syndrome, or congenital anomaly consistent with the reported incidence of syndromic patients with cryptorchidism [2,3]. The standard of care at UCSF is to offer orchiopexy to all patients with cryptorchidism regardless of associated syndromic comorbidities as long as medically cleared by pediatric anesthesia. It has been our experience that parents of such children often pursue orchiopexy as it may confer a sense of positive impact over the patient's complex medical circumstance. In addition, families feel that they can exercise control over the decision for their child to undergo orchiopexy with positive clinical outcome. This is often in the setting of other comorbidities that may otherwise not have as rectifiable of a clinical outcome. Consequently, orchiopexies are routinely performed at UCSF on children with significant deficits (i.e. syndromic presentations often requiring auxiliary support such as G tubes, tracheostomies and/or patients with cognitive and motor developmental delay.) but there exists no literature on patient characteristics and clinical outcomes compared to non-syndromic patients.

Our study supports the hypothesis that orchiopexy is safe in syndromic patients compared to an age-matched control group.

Specifically, there were no intraoperative complications and a small but comparable rate of minor perioperative complications. This finding is helpful in counselling both patients and patient families of the relatively minimal risk of orchiopexy requiring general anesthesia even in patients that may have significant syndromic comorbidities.

Of note were differences in the incidence of bilateral orchiopexies compared to the control group. Both children with developmental delay and genetic syndromes had a significantly higher rate of bilateral orchiopexies compared to the control group (Tables 1 and 2). Previous case reports have noted incidence of bilateral cryptorchidism in patients with various syndromes (i.e. Down's, Persistent Mullerian Duct Syndrome) though there does not exist a high-powered study that demonstrates higher incidence of bilaterality. Given the impairment of the physiologic hypothalamic-pituitary-gonadal axis that often occurs in several of these syndromes and the importance of hormonal signaling to guide testicular descent, differences in bilateral cryptorchidism are understandable.

Similarly, it is not surprising that patients with genetic syndromes had statistically higher chance of requiring a two-staged procedure. This could be explained by the known higher incidence of intraabdominal testis in syndromic patients, for example in

those with Prader Willi and Noonan's syndrome [13,14].

Limitations of our study include the relatively short longitudinal follow-up limiting the ability to evaluate other covariates of interest when comparing syndromic patients to their age-matched control. Specifically, we were not able to evaluate whether patients in our syndromic cohorts demonstrated differences in long-term fertility, malignancy occurrence, or testicular atrophy status post orchiopexy compared to control patients. Another limitation of this study is that it was performed at a single institution that specializes in the management of complex pediatric conditions, including orchiopexy. This includes expertise in patients with complex medical conditions and pediatric anesthesia. Multi-institutional studies and community based studies would add additional support to the original hypothesis that syndromic patients with cryptorchidism have similar outcomes to non-syndromic patients.

Conclusions

Clinical outcomes were no different between patients with syndromes undergoing orchiopexy compared to non-syndromic children. Patients with non-specific developmental delay and a genetic syndrome more often had bilateral orchiopexies. Patients with a genetic syndrome were also less likely to have a single stage procedure. Orchiopexy in syndromic patients undergoing orchiopexy is safe with comparable outcomes to non-syndromic patients.

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